**EXHIBIT D**

Translation of Luderschmidt et al. response of 17 March 1998 to the German Patent Office

Opposition against German Patent No. 44 47 287.0-41
Patentee: Cevc, Gregor, Prof. Dr.
Opponent: ROVI GmbH
Preparation for the transport of active agents through barriers

In response to the submission of the Patentee of 11 July 1997, wherein the Patentee has responded to the Opposition of the Opponent of 6 February 1997.

The statements of the Patentee in the above-cited submission are not suitable for questioning the request for total revocation of German Patent 44 47 287.0-41 (designated as the attacked patent in the following) requested by the Opponent.

In the following, the designation of the claim features according to the feature analysis under item I of the opposition grounds of 6 February 1997 are maintained.

I.

A.

In his argumentation concerning an inadmissibility of the opposition grounds in the meaning of § 59 Sec. 1, Sentence 4, German Patent Law, the Patentee relies in detail on the BGH (German Federal Supreme Court) decisions "Sortiergerät", "Streichgarn", "Alkyldiarlylphosphin" and "Epoxidations-Verfahren". However, 3 of these 4 decisions are not applicable in the present case.

The decision "Streichgarn" relates an alleged but not proven prior use in the context of a method of production. In the decision "Alkyldiarlylphosphin", the opposition grounds did not have any recognizable relation to the prior art in detail, which would have had to be the base for evaluating inventive activity and progressiveness of the patented invention. In the decision

"Epoxidations-Verfahren" the opposition grounds only dealt with one partial aspect of the protected invention, but not with the patented teaching in total, so that the formal incompleteness of the opposition grounds was treated like opposition grounds relating to a teaching which is not protected.

However, what the Patentee partially cites in the first paragraph on page 2 of their submission concerning the interpretation of the decision "Sortiergerät" is only half of the truth. For example, it is also noted by the Senate in this decision,

> *"that...in some particular single cases, the citation of patent- or laid-open documents only by number, or of documents only by their bibliographical origin, may be sufficient as arguments for supporting an opposition based on lack of patentability...However, the Senate correctly emphasizes that a more detailed argumentation may only regarded as non-essential in those cases, where the context is self-explanatory for an experienced reader from a short text passage and "actually suggests itself" and "catches the eye", as a proof for the alleged opposition ground. Only in such special cases, does the a simple naming of the prior art form a sufficient basis for a final statement by the Applicant and for a final judgment by the Patent Office. Thus, one can only think about very clear and simple-structured cases."*

How very clear and simple the situation is in the present case is shown as follows:

B.

Referring to page 5, second paragraph of our opposition grounds, the Patentee argues in his response letter (page 3, paragraphs 2 and 3):

*"Thus the Opponent generally states that the features A and B, which form the generic term of the independent claims 1 and 22, have been taken from D1....However, the Opponent provides no indication enabling someone (whom?) to finally judge on these assertions without investigations on his own, based on the cited prior art D1-D5. For Example, the Opponent has missed to indicate, at which part of D1 one can learn that the carrier substance comprises at least two (physico-chemically) different components (feature B)."*

Concerning this, it has to be stated:

1. D1 is a patent of the Patentee of the attacked patent.

2. D1 is mentioned in the attacked patent as prior art, moreover as closest prior art, which formed the basis for the object to be solved by the attacked patent (see page 3, lines 20-38) (see also our opposition grounds, page 4, first full paragraph).

3. The questionable features A and B are the two features of the generic terms of the independent claims 1 and 22 of the attacked patent.

4. For forming the features of the generic terms of a claim, the following general criteria are valid (cf. for example, Schulte, Patent Law, 5th ed., § 35, Nos. 50a-f):
   i) The features have to be known from a single prior art document;
   ii) The relation of the features to each other has to be disclosed;
   iii) The features of the generic term have to be features of the invention, too.

Beyond this background, is it allowed for an experienced reader to set out from the point that features A and B according to claims 1 and 22 of the attacked patent may not be included in D1? Furthermore, if these arguments of the Opponent, which are based on obvious

requirements for forming generic terms of claims 1 and 22 are called "assertions" by the Patentee, and the evaluation of which are not possible without investigations on one's own, one will have to conclude that the Patentee was not sure, and still is not sure, about the formation of his generic terms.

In this context, it has further to be pointed out that the term "physico-chemically" in feature B is a meaningless word which does not say anything. The Patentee should tell us only one combination of two different components, which do not differ physico-chemically from each other! If they did not do so, they certainly would not be two different components (in the meaning of parts of a whole), rather they would be identical!

C.

Concerning feature C, the Patentee states that no further comments are necessary to the question that without further investigations the contention cannot be evaluated that feature C is fulfilled in view of the possibilities of combinations given in D1. This statement is really astonishing. First of all, it has to be remarked that the "investigation of the circumstances" in the BGH decision "Sortiergerät", which the Patentee aims at in this context, refers to the establishment of a technical relationship between the subject matter of the attacked patent and the content of the named document.

The corresponding assessment of the Patentee in his counterstatement is then astonishing insofar as it lets us have an insight in the fact that Patentee does not know what to do with his own disclosure provided in the attacked patent. The possibilities of combinations derivable from D1 really form an integral part of the disclosure of the attacked patent! One simply has to compare the corresponding text in the attacked patent, on page 5, line 15 to page 6, line15, with the corresponding text in D1 on page 4, line 55 to page 5, line 55. The fact that in the formula (2) in the attacked patent compared to the corresponding formula (2) in D1 does not

contain a methylene group anymore, has no affect on the factual (not formal) identity of the disclosure of these documents.

Furthermore, if one can learn from the attacked patent on page 6, lines 44-46, that all compounds mentioned as surface-active in D1 (more than 7 1/2 pages in total!) are suitable, then all possibilities of combinations in D1, which one can think of (even including the active agents mentioned in D1 (see attacked patent on pages 51-52)) are inherently disclosed in the attacked patent. However, the fact that the Patentee himself, in order to verify the statement that among the multitude of potential possibilities of combination, certainly a large number will fulfill feature C, has to make his own investigations first, leads to only one conclusion: the Patentee does not trust in the disclosure of his own patent!

On the other hand, even this intention, to determine at least two components fulfilling feature E of claim 22, on the basis of the disclosure to the attacked patent,, with his own investigations, but without the need of his own inventive activity by the Patentee, is demanded of a person skilled in the art, who is a priori not yet familiar with the "novel" subject matter of the patent. Accordingly, this is necessary to fulfill the requirement of patentability according to § 35 II.

However, a person skilled in the art who is not familiar with the "novel" invention can relatively easily find out combinations of at least two compounds disclosed in D1 (and in the attacked patent accordingly) which fulfill feature C of claim 1, or feature E of the method claim 22, respectively, but because of the fact that the Patentee himself, who is very familiar with the invention, has to make additional investigations of his own, his statements obviously provide an indication that the corresponding disclosure cannot be complete!

According to the attacked patent, on page 4, lines 38-43, one can classify the components also by their HLB values, instead of the solubility differences of the components, which should

then, in order to fulfill features C or D, respectively, differ by more than 2 (up to maximum 10) HLB value units. For finding suitable components, only a table of compounds classified by their HLB units is necessary. Such a (simple) table is, e.g., Table IV on page 36 of D2. In this Table, components with HLB values of 5-16.7 are disclosed. Some of the components disclosed in D1 may be easily identified out of these corresponding components, in particular by their trade names. These are, in particular, Span 20 (page 13, line 31 of D1), Triton X-114 (page 13, line 6), Brij 76 (page 7, line 1), Brij 56 (page 6, line 59), Nonidet P-40 (page 13, line 11), Triton X-100 (page 13, line 10), Tween 60 page 13, line 26), Tween 80 (page 13, line 26), Tween 40 (page 13, line 32), Brij 58 (page 6, line 59) and Tween 20 (page 13, lines 15 and 25). Of these components with HLB values between 9 and 16.7, two components are easily selectable, which differ by more than 2 unites, so that features C or E, respectively, are fulfilled.

D.

It is not understandable what the Patentee states on page 3, last paragraph concerning feature D.
It is expressly pointed to the important technical feature "point of solubilization" which should neither have been mentioned, nor discussed in this context in the opposition grounds. However, where is this important feature discussed in the attacked patent, due to its particular importance? In the attacked patent, the solubilization is mentioned on page 3, line 48, but only as an alternative condition, on page 4, line 6, where it is disclosed that transfersomes may be formed from combinations of any components independently of their capability of solubilization, and on page 4, lines 17-18 and line 67, where they once again appear as an alternative condition.

However, where this allegedly technically important feature of the attacked patent, which should have to be discussed, in the Patentee's opinion, does not find any mention at all, is

where the relevant statements for the production of "inventive" transfersomes is discussed, e.g. on page 7, line 66 to page 8, line 26, or in any one of the examples. Here, the adjustment or determination of the allegedly so very important feature "point of solubilization" should have been disclosed, at least once, in order to enable the skilled person to determine if feature D of claim 1 is indeed fulfilled, or not!

II.

The statements of the Patentee concerning support of the opposition under item III of his submission do not have any affect.

A.

First of all, it is pointed out that the reasons of the Opponent (in its opposition grounds) are mostly based on contentions and statements, which do not deal with the features of the claims. Then, it is expressly emphasized that the opposition grounds are provided in § 21 German Patent Law *in toto*.

Here, the Patentee holds a strange legal opinion, in that he draws up a correlation of the opposition grounds according to § 21 German Patent Law, only with a relation to the features of the claims.

In §21 I German Patent Law, 4 revocation grounds are mentioned *in toto*, among them at the second position, the indication that a patent may be revoked according to § 61, if it can be shown that a patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a skilled person. This requirement of patentability is derived from § 35 II German Patent Law, where it is stated: "The invention has to be

disclosed in the application in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art".

According to § 35 I 2-4, the application to be disclosed also comprises the description and the drawings, besides the patent claims. If the Opposition, as in the present case, is also based on the opposition ground of § 21 I 2 German Patent Law, the description (and not only the claims) has also to be examined for its disclosure.

It is, however, interesting in this context, what the Patentee states about the unclarified questions to the disclosure of the attacked patent, which are asked under point IV in the opposition grounds, in his counterstatement. There is not even one letter in the whole counterstatement of the Patentee, indicating that there was the slightest attempt to clarify these unclarified questions. These not disclosed features are, after all, *inter alia*, the unambiguous determination of the permeability or the capability of permeation, which is an indispensable prerequisite for adjusting the content of amphiphilic components!

The statements of the Patentee instead deal with inapplicable assessments of the documents presented by the Opponent, together with the opposition grounds, at most.

B.

If it is pointed out that contrary to the present invention the amount of surface-active substance in D1 is selected, with full awareness, in such a way that one approaches the point of solubilization, this contention is in complete contrast to the disclosure of D1. If one only looks at claim 2 of D1, which should be a preferred embodiment, it has to be recognized that the amount for the surface-active substance should be

- at least 0.1 mol %
- **in particular** between 1 and 80 mol %

- **preferably** between 10 and 60 mol %
- **especially preferred** between 20 and 50 mol %

of the amount of surface-active substance, which causes solubilization. One can then read from the upper limit of these ranges that the tendency is away from a particularly close proximity to the point of solubilization.

Accordingly, the amount of surface-active substance according to claim 1 of D1 is not adjusted in relation to the point of solubilization, but according to the maximum permeation capability, at which the amount shows a certain proximity to the amount at point of solubilization (which is defined by no parameter). In contrast to the discussion of D1 in the attacked patent (page 3, line 22) there is no lower limit (like $\geq$ 0.1 mol % in claim 2) in claim 1 of D1 for such an amount, but only a upper limit of $\leq$ 99 mol %. Thus, it follows that if a transfersome according to claim 1 of the attacked patent has a maximum permeation capability at an amount of, e.g. 0.05 mol % of surface-active substance, referring to the amount of this substance at the point of solubilization, then this transfersome fulfils the condition according to feature D1) of claim 1 of the attacked patent, as well as the condition of the characterizing feature of claim 1 of D1. This has to be so, since the amount of 0-5 mol % of surface-active substance is so close to the amount of this substance and the point of solubilization ( the proximity is not defined in D1 by numbers!) that the transfersome has a maximum penetration capability at a stability which is still sufficient.

C.

In the context of the determination of the disclosure of D2, it is stated that there is no indication in this document on how to adjust the amount of solubilizing components, in order to obtain an optimal penetration capability according to claim 1 of the attacked patent. However, neither claim 1 nor method claim 22 of the attacked patent includes information or a condition for optimal penetration capability in any feature. Obviously, for adjusting the

amount of the solubilizing components, a quantitative value for the penetration capability should then be determinable, in the Patentee's opinion. Concerning this lack of disclosure of the attacked patent, see our statements and questions in the opposition grounds on page 9 to 13.

Further, in the context of D2, the Patentee states that there is no indication that the components should differ in their solubility, for example in water, by a factor of 10. For evaluating novelty or inventive activity of a subject matter of a patent like in claim 1 of the attacked patent, it is, however, not relevant if a property to be analyzed therein has been adjusted specifically and nothing else, or if this property is the result of pure chance. One cannot see from a subject matter, and it is not determined under any circumstances, if, for example, a present component composition has been adjusted on the basis of any parameters in such a way; the only thing is that the relevant parameter are included in such a way and by nothing more.

In the relevant ternary phase diagram according to Fig. 5 of D2 (page 42) two (naturally physico-chemically) different components are included besides water, namely lysolecithin and lecithin, one of which is insoluble and swellable (Class II) and the other one is soluble of the Type A, Class $III_A$. As is unambiguously disclosed in the context of D2, the insoluble component of Class II is lecithin (page 42, second line from below, above Fig. 5) having a solubility of approx. $10^{-10}$ M (page 34, lines 1 and 2) and the soluble component of Class $III_A$ is lysolecithin having a solubility of approx. $10^{-2}$ M (page 31, last line above Table 1 and Table 1, Class III(A)). Feature C of claim 1 of the attacked patent is thus unambiguously disclosed in Fig. 5 of D2.

Thus, Patentee's contention is surprising that the ternary phase diagram according to Fig. 5 of D2 is not transferable to the inventive systems of the attacked patent, because the phase diagram of D2 is disclosed for a temperature of 52°C, while the inventive systems of the

attacked patent commonly show 32°C (skin temperature). Where in the attacked patent has a temperature of 32°C ever been disclosed? On the contrary, as already pointed out in our opposition grounds on page 10, last paragraph, only two temperatures are provided, namely in Examples 1-4, one of 62°C and in Example 7, a temperature of 52°C (sic!) However, if already systems of different temperatures are not transferable into each other, a temperature of 32°C must obviously be an essential feature, which however is not disclosed in the attacked patent. Consequently, this is a further lack of disclosure!

D.

The statements of the Patentee as to the relevance of the cited document D3 are not understandable. As known, D3 relates to the same technical field, namely, the preparation of active substance carriers (i.e. even for transport of active agents) through barriers, like e.g. skin (see e.g. p. 104, middle column: *"...Permeability in the case of a depot drug carrier like liposomes..."*; or page 105, left column:"*...Penetration of small liposomes through the sinusoidal windows of epithelial cells and direct absorption in the cells of parenchyma....*"; or page 106, left column: "*...liposomal packaged insulin to be administered buccal...*")

The mentioning of these drug carriers, whether as "transfersomes" "liposomes", "Adam" or "Eve", is finally not suitable to function as a differentiating feature, because it is only a question of naming. It is only important that it concerns the same technical field.

E.

Even the opinion of the Patentee as to the importance of D4 and D5 is untenable in this form. These documents indeed disclose a feature which is the subject matter of the patent and claims, namely feature Da) of claim 1. D4 and D5 document the known fact in the prior art that, e.g. with the use of commercially sold soya lecithin, which certainly is used in Examples

1-25 of the attacked patent (designated there as phosphatidylcholin) shows such chemical contaminations (see also D2, page 35, first paragraph), so that without any further information about a lower limit for these components according to feature Da) (< 0.1 mol %) and without any indication about purity criteria for these components in the attacked patent, the feature Da) is inherently fulfilled when using commercially available soya lecithin (in Examples 1-4, the purity is given with about 98%, in Examples 5-6 with "purer than 95% ".

III.

Since the Patentee has provided no clarifying information to the questions raised under item IV of the opposition grounds in his counterstatement, it is requested that these questions should be clarified before making the decision, either in written form or in oral proceedings, precisely naming each position in the disclosure of the attacked patent.

The request to revoke German Patent 44 47 287.0-41 in its entirety is maintained.

Signed by Dr. Luderschmidt, Patent Attorney